REMARKS

Claims 1-4, 14, 24, 25 and 30 are being examined and have been rejected. Applicants had previously elected the species of SEQ ID NO: 1 for examination. Applicant acknowledges that the search has been extended to include SEQ ID NO: 5. New claims 33 – 42 have been added and claim 14 has been canceled.

Corrections to the Specification

Applicant has corrected the specification to include designations of sequence numbers where the sequences occur.

In addition, Applicant submits herewith a new Declaration of inventor Flyer.

Applicant has also corrected the specification to include designations of registered trademarks where they occur.

The specification was also corrected at page 46, line 18, to replace "Hsp56" by "Hsp65" in accordance with the Examiner's suggestion in ¶15 of the Office Action.

Rejection Under 35 U.S.C. §112, ¶1 – Written Description

Claims 1-4, 14, 24, 25 and 30 have been rejected under 35 U.S.C. §112 as failing to meet the written description requirement.

The rejection faults the Applicant in that the specification is claimed to not covey to the Artisan that the Applicant had possession at the time of invention of the claimed immunogen, pharmaceutical composition and vaccine thereof. It also contends that the

instant claims encompass an immunogen or an isolated peptide. The main thrust of the rejection appears to be that the specification does not disclose any immunogen comprising SEQ ID NO: 1, 2, 3, 4 or 5 or any of the subgenera encompassed by the claims and that it does not adequately describe the scope of the claimed genus in that recited immunogen could be of any length and is not limited to flanking sequences found in the proteins of origin.

In response, Applicant has amended claim 1 to recite a molecule that induces a CTL-response and that comprises one or more copies of the recited peptides.

Applicant notes that the term "immunogen" is defined in the application as being a molecule that induces a CTL response (see application at page 9, lines 1-7). Because the original claim recited an immunogen and the specification notes that an immunogen is such a molecule, the amended claims are still within the elected group. Claim 1 has been amended to recite only sequence 1 but applicant still contends that the remaining sequences should be included.

In addition, claim 2 has been amended to recite SEQ ID NO: 1.

Claim 14, directed to a vaccine, has been canceled.

Claim 24 has been amended to recite an isolated polypeptide having the recited sequences, claim 25 has been amended to recite SEQ ID NO: 1.

Claim 30 has been amended to delete the term "suspended."

New claims 33-42 have been added, which are drawn to a molecule possessing the structural features of claim 1. This is supported in the application at page 9, lines 5-7.

In sum, no new matter has been added and all pending claims lie within the

elected group and species.

Because the effect of these amendments is to recite the peptides and molecules actually recited in the application, Applicant believes that the written description has been complied with.

The Examiner has also argued that Applicant has not disclosed any immunogens in the specification. Applicant responds that, within the disclosed invention, the exact nature of the immunogen is not important. Applicant has provided both structural and functional features of such a molecule. Thus, the immunogen of claim 1 must comprise one of the peptides of SEQ ID NO: 1 or a peptide differing by no more than 1 amino acid from SEQ ID NO: 1. This could include the sequence of SEQ ID NO: 1 with one additional residue (a decapeptide) or one residue removed (an octapeptide) wherein said difference is due only to a conservative amino acid substitution, or an addition or deletion. Such an immunogen or molecule obviously constitutes an oligopeptide or polypeptide comprising one or more copies of the recited sequences. Because synthesis of such molecules has been well known in the art for quite some time, those in the art could hardly doubt that Applicant was in possession of such structures at the time of the invention.

In addition, the functional limitation recited by Applicant is that the claimed molecule elicits a CTL response. The peptides claimed by Applicant were isolated by this very ability (see application at page 45, Example 4). In addition, the assay for such stimulation of a CTL response is simple and straightforward with no undue experimentation being required. The fact that various structures are routinely tested is not something that rises to the level of undue experimentation, even where such testing is extensive, so long as it is routine. Applicant believes that those skilled in the art know how to test such molecules once they are told what peptide sequences to incorporate (see, for example, the Kubo et al patent (U.S. 5,662,907, cited by the Examiner herein and wherein CTL-induction is the only recited use, along with simple and straightforward assays well known to those skilled in the art).

What is not known to those skilled in the art is what peptide sequence is capable of stimulating a CTL response that is reactive with a peptide naturally presented by the target infected cell. Applicant teaches several in the present application, one of which is in claim 1. As a result, Applicant believes that those skilled in the art would believe Applicant to be in possession of the claimed invention.

Rejection Under 35 U.S.C. §112, ¶1 - Enablement

Claims 1-4, 14, 24, 25 and 30 have been rejected under 35 U.S.C. §112 as failing to meet the enablement requirement.

The Examiner has argued that Applicant provides little information as to how to make and use the claimed invention. Applicant disagrees.

The Examiner first argues that the state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed immunogens/vaccines/peptides or compositions can be made and used therapeutically or prophylactically and that no working examples are disclosed. (see page 5 of the office action, lines 14-18)

In response, Applicant first notes that the present invention relates to MHC Class I epitopes of a given structure and length (see application, page 9, lines 8-11) because early TB infection is an MHC Class I process and not MHC Class II like other microbial infections. (see application, page 5, lines 3-13)

In order to be patentable, Applicant's immunogens/peptides need have only at least one use. One such use, and the means to assay such use, is described in the application at page 33, line 18, over to page 34, line 17. Such a use is further described and enabled by Example 4 (page 45). In furtherance of this, Applicant has also added

new claims 33-42, directed to a CTL-inducing molecule having the structural limitations of claim 1 and useful in identifying CTLs that recognize the claimed epitopes. Such a molecule is described in the specification as being encompassed by the term immunogen and is therefor within the elected group. (see application at page 9, lines 5-7)

Here, Applicant has provided a use and a method of carrying out that use and no more is required. Such uses for the peptides disclosed by Applicant are well known to those skilled in the art, as well as searching for sequence variability. For example, see the Kubo et al patent cited in the office action, especially at columns 7, 8 and 9, where methodology similar to Applicant's is disclosed. Applicant teaches such methodology in the application via the fact that such methods were used by Applicant to identify the disclosed epitopic peptides (such as in Example 4, page 45).

The Examiner also contends that the application does not disclose an immunogen. In response, Applicant notes that the application teaches the proteins in which some of the peptides were found and that these, except for Hsp65, may be immunogenic. However, applicant defines the term immunogen as including a molecule that induces a CTL response, which may be *in vitro* (as described in the application at, for example, page 33, lines 11-15). The Examiner is reminded that the claims under examination are composition of matter claims and not method claims (the latter are withdrawn claims) so that pointing to various uses believed not to have been enabled is not relevant so long as at least one use has been. In short, if the Examiner's contention is that no use has been enabled then Applicant could not have identified these CTL-specific epitopic peptides at the outset.

Applicants respectfully remind that the issue here seems to be that the Examiner rejects use of SEQ ID 5 in a composition of matter claim because the identical sequence (TLLQAAPTL) was predicted as a CTL epitope in SwissProt_42 Accession No P06806 based on an algorithm used for this purpose. However, the algorithm does not allow one to determine whether a predicted peptide is actually produced and

presented by a cell. The present invention demonstrates that this is indeed the case for SEQ ID 5.

The Examiner also argues that use of "comprising" fails to disclose wherein the peptides constitute a CTL epitope and additional sequences that are not a CTL epitope. Applicant's response is that this situation is the natural result of "comprising" language. Applicant does not have to state what additional materials may be present. Applicant provides structural limitations for the claimed epitopes along with assays for detecting binding to CTL sites – more is not required. The point of invention is the epitopic sequence (for example, the nonapeptide sequences of SEQ ID NO: 1 and 5) and any additional CTL-inducing sequences that are built around those sequences. The fact that numerous assays may be run to determine a proper CTL-inducing molecule does not rise to the level of undue experimentation. In sum, Applicant has provided a useful structural framework with which to begin (for example, the epitopic sequences disclosed in the application), structural limitations for guidance (between 8 and 14 residues in length and having only conservative amino acid substitutions) and a functional limitation (inducing a CTL-response, which may be *in vitro*). This is believed to be sufficient guidance for those truly skilled in the art (and probably more than they need).

The Examiner also argues that the length of the peptide is important for HLA binding (citing the Engelhard paper, which author is one of the named inventors of the present application). In response, Applicant notes that such considerations are in the claims along with other guidance in the application. Thus, all of these considerations have been mentioned in the application and dealt with in the art already, as shown by many of the references cited by the Examiner as bearing on the application. In sum, these considerations are already known to those skilled in the art and it is such a consideration that facilitated identifying the peptides of the claimed invention.

The Examiner's conclusion that the application contains insufficient guidance as to how to make and use the claimed invention is interesting in that the Examiner cites a

number of references, many of which disclose similar compositions of matter with apparently no difficulty in how to make or use them. In particular, the Examiner cites: "Mohagheghpour et al teach importance of CTL in protective immunity against M. tuberculosis ..." (Page 8 and again Page 9 of the Office Action); and, "Mohagheghpour et al teach that their findings are relevant for both vaccine development and adoptive immunotherapy." Also, "U.S. Patent No. 5,662,907A discloses that immunogenic peptides can be introduced into a host, including human, as a homopolymer of active peptide units, especially when being used in a vaccine composition (especially column 12)." (Page 9 of the Office Action) Applicants respectfully remind that the invention is based on knowing which sequences to utilize and that is taught by Applicants.

Rejection Under 35 U.S.C. §112, ¶2

Claims 1-4, 14, 24, 25 and 30 have been rejected under 35 U.S.C. §112 as being indefinite.

Claim 1 was found to be indefinite because of use of the terms "amino acid units" and "amino acids" in different portions of the claim. In response, claim 1 has been amended to recite "amino acid residue" as suggested by the Examiner.

Claim 3 was found indefinite for lack of antecedent basis in use of the phrase "one or more of said peptides" and for use of the phrase "immunogen segment." In response, claim 3 has been amended to delete the term "segment" and recite only "immunogen" while use of "one or more of said peptides" is believed appropriate in view of the amendment to claim 1.

Claim 14 was rejected for grammatical errors. This claim has been canceled.

Claim 24 has also been amended, per the Examiner's suggestion, to use the phrase "amino acid residues."

Claim 25 has been amended to cancel the term "oligopeptide" per the Examiner's suggestion.

Rejection Under 35 U.S.C. §103

Claims 1, 2, 4, 14, 24, 25 and 30 have been rejected under 35 U.S.C. 103(a) as being unpatentable over SwissProt_42 Accession No. P06806 in view of Mohagheghpour et al (J. Immunol., 161:2400-2406 (1998) and Rupert et al (Cell, 74:929-937 (1993)).

Initially, Applicant notes that the Examiner indicates (paragraph 11 of the Office Action) that for "the purpose of prior art rejections" the limitation "wherein said immunogen is not hsp65 protein" does not appear in priority application 60/255,292. Applicant does not believe that absence of such limitation is relevant to prior art rejections, since Applicant is always free to insert any limitation disclosed in the application as filed for purposes of avoiding prior art (since such limitation was in the application as filed, no new matter is added thereby and the dates of priority cases versus prior art references is of no relevance).

A finding of obviousness requires three conditions:

In response to the rejection for obviousness, this rejection appears directed solely to SEQ ID NO: 5.

1. The cited references, in light of the then available general knowledge, must suggest the combination of the references to produce the claimed invention [see: *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988)].

2. Combination or modification of the references must have a reasonable expectation of success. [See: *Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209 (Fed. Cir. 1991)]

3. Combination of the cited references must teach or suggest all of the limitations of the claim(s) [See: *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970)]

Applicants note that the reference to Swissprot_42 is a reference to a much larger protein sequence that provides no hint of the sequence of SEQ ID NO: 5 as being in any way important. This sequence is not recited in the other two references relied on by the Examiner. As noted above, the combination of the references must suggest the claimed invention with reasonable expectation of success and must teach all of the limitations of the claims. Applicants contend that that is not the case.

Applicants have amended claim 1 as noted above. Rupert et al is offered by the Examiner only to suggest the use of peptides of certain length or having certain amino acids at specified positions, much of which Applicants believe is known. In addition, Applicants' SEQ ID NO: 1 does not meet the Ruppert criteria in that there is no L or M at residue 2. Thus, the basic invention must be rendered obvious by combination of Swissprot_42 and Mohagheghpour et al. The latter reference certainly makes no mention of Swissprot_42 as a likely candidate for finding immunologically useful peptides. In addition, their test utilized dendritic cells, which contain MHC Class II molecules. As noted by Applicants, early in the infectious period, tubercle organisms are found in vacuoles of phagosomes and present as MHC Class I molecules instead of class II. Thus, those skilled in the art may not be motivated to search for immunogens of the present invention using the teaching of Mohagheghpour et al.

In particular, to the extent that this ground of rejection is based on use of an algorithm in SwissProt_42 Accession No P06806, such algorithm cannot predict the

discovery of the present invention, that this peptide is actually processed and presented by cells in which the parent molecule, the 65kDa antigen, is expressed. It is this finding that enables use of the peptides of the invention as immunogens.

Further, if the Examiner's position is that it would have been obvious to look for any kind of peptides from all manner of proteins in order to find usable epitopes then Applicants respond that this is essentially an "obvious to try" type of rejection and that is not the standard for showing *prima facie* obviousness. (see *In re Geiger,* 2 USPQ 2d 1276, at 1278 (Fed. Cir. 1987) where the court found no prima facie case of obviousness where, based on the prior art, it might be obvious to try various combinations of known agents to achieve the desired effect) In the present case one would have to search numerous proteins at great cost and effort to locate the specific peptide sequences provided by the Applicants' teaching.

Claim 3 was rejected under 35 U.S.C. 103(a) as being unpatentable over SwissProt_42 Accession No. P06806 in view of Mohagheghpour et al (J. Immunol., 161:2400-2406 (1998) and Rupert et al (Cell, 74:929-937 (1993)) and further in view of U.S. Patent No. 5,662,907.

In response, Applicant contends that this claim can only be obvious if claim 1 is obvious and for the above-reasons it is not. Claim 1 has been amended to recite use only of SEQ ID NO: 1 and therefor reliance on references other than the '907 patent are mooted. Because claim 3 depends from claim 1, if claim 1 is patentable then any dependent embodiment thereof should also be patentable.

In view of the above-recited amendments and remarks, Applicants believe that the grounds of rejection have been overcome and request re-consideration of the pending claims.

Applicants have included herewith a request for a 3 month extension of time to respond and a check for the required fee. The Commissioner is authorized to charge payment of any fees required under 37 CFR 1.16 associated with this communication or credit any overpayment to Deposit Account No. 03-0678.

FIRST CLASS CERTIFICATE

I hereby certify that this correspondence is being deposited today with the U.S. Postal Service as First Class Mail in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Alan J. Grant 4/27/05
Alan J. Grant, Esq. **Date**

Respectfully submitted,

Alan J. Grant

Alan J. Grant, Esq.
Reg. No. 33,389

CARELLA, BYRNE BAIN, GILFILLAN,
CECCHI, STEWART & OLSTEIN
5 Becker Farm Road
Roseland, NJ 07068
Phone: 973-994-1700
Fax: 973-994-1744